

A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues

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Summary

Background The steady worldwide increase in the incidence of non-Hodgkin lymphoma during the past few decades remains mostly unexplained. Several studies suggest that there may be an association between the agricultural use of the organochlorine 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) and increased risk of non-Hodgkin lymphoma. We have investigated the association between risk of non-Hodgkin lymphoma and body burden of selected organochlorines in the general population in a nested case-control study.

Methods We measured prediagnostic serum concentrations of DDT, its metabolites, and other organochlorines, including polychlorinated biphenyls (PCBs), in 74 cases of non-Hodgkin lymphoma and 147 matched controls identified from a prospective cohort of 25 802 adults, established in 1974 in Washington County, Maryland, USA. We report results for total lipid-corrected serum concentrations of DDT and total PCBs.

Findings There was a strong dose-response relation between quartiles of total lipid-corrected serum PCB concentrations and risk of non-Hodgkin lymphoma overall (odds ratios by quartile: 1.0; 1.3 [95% CI 0.5–3.3]; 2.8 [1.1–7.6]); and 4.5 [1.7–12.0]; *p* for trend=0.0008) and separately in men and in women. There was also evidence suggesting that seropositivity for the Epstein-Barr virus early antigen potentiated the effects of serum PCBs. By contrast, total lipid-corrected serum concentrations of DDT were not associated with risk of non-Hodgkin lymphoma.

Interpretation These results should be regarded as hypothesis-generating. Before causal inferences can be made about exposure to PCBs and increased risk of non-Hodgkin lymphoma, our findings require replication and the biological plausibility of the association needs further investigation.

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Introduction

Increases in the incidence of non-Hodgkin lymphoma have been documented since the late 1940s in the USA,¹ and since the 1960s in the UK² and other countries worldwide.¹ Changes in diagnostic patterns, use of immunosuppressive drug treatments, and rates of HIV infection account for some of this increase, but a substantial part remains unexplained.^{1,3} Our investigation was motivated by observations of an association between the agricultural use of the pesticide 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) and increased risk of non-Hodgkin lymphoma.^{4,6}

In this case-control study, we measured serum concentrations of DDT, its metabolites, and other organochlorine compounds including polychlorinated biphenyls (PCBs) in stored serum samples from cases of non-Hodgkin lymphoma and matched controls identified from a population-based prospective cohort study established in 1974 in Washington County, Maryland, USA. We examined the association between risk of non-Hodgkin lymphoma and serum concentrations of these compounds, with a particular emphasis on total lipid-corrected serum concentrations of DDT and PCBs.

Methods

Study population

Between August and November, 1974, 25 802 adults were enrolled in the Campaign Against Cancer and Stroke (CLUE I) in Washington County, Maryland, USA, which was sponsored by the Johns Hopkins University School of Hygiene and Public Health. A 15 mL blood sample, a blood-pressure measurement, and answers to a brief questionnaire were obtained from participants. Serum was separated and stored at -73°C. A second blood-collection survey was conducted in 1989 in Washington County for the Campaign Against Cancer and Heart Disease (CLUE II); about 25% of individuals who enrolled in CLUE I also took part in CLUE II.⁷

Cases

All cases of non-Hodgkin lymphoma were identified from the Washington County Cancer Registry. The incidence of non-Hodgkin lymphoma in Washington County (10.9 per 100 000 person-years) estimated from cases identified by the Cancer Registry between 1975 and 1989 is similar to the median incidence rate based on data from the Surveillance, Epidemiology and End Results (SEER) program for this period.⁷ We defined a case as a CLUE I participant with histologically confirmed non-Hodgkin lymphoma (ICD-8 code 200 or 202) first diagnosed between Jan 1, 1975, and May 31, 1994, who did not have a history of cancer, apart from non-melanoma skin cancer, before the diagnosis of non-Hodgkin lymphoma.

We identified 87 eligible cases. Serum samples from 11 cases were not available for our study because all the stored samples had already been used for testing in previous studies. The demographic characteristics of these 11 cases were similar to those of the remaining 76 cases, except that non-Hodgkin lymphoma had been diagnosed, on average, several years earlier.

Of these 76 cases, 51 had slides available for pathology. On review, two of the 51 cases were judged not to be non-Hodgkin lymphoma (one Hodgkin's disease and one hairy-cell leukaemia). Thus, 74 cases were available for the study.

Controls

Eligible controls for each case were individuals who were alive and did not have cancer (with the possible exception of non-melanoma skin cancer) at the time of case diagnosis. Two controls were selected for each case and matched according to: race, sex, date of birth (within 1 year), participation in CLUE (CLUE I only or CLUE I and CLUE II), date of blood-sample donation (within 15 days), participation in private censuses conducted by the Johns Hopkins University Training Center for Public Health Research in 1963 and 1975, and location of stored blood specimen (Hagerstown or Baltimore, MD). If adequate samples of serum were not available for a control, which occurred in less than 3% of controls, another individual was selected as a control by means of the same criteria. We matched cases and controls according to participation in the CLUE cohort so that concentrations of organochlorine from individuals who provided blood samples in both studies could be compared in future analyses. Participation in private censuses was also included so that demographic data from these surveys could be used to adjust study results; however, we were not able to use this information because of missing data for a substantial number of participants.

Organochlorine analysis

Serum samples were arranged in sets that consisted of one case and two matched controls in random order. Samples were thawed, separated into 1.5 mL volumes, and immediately refrozen on dry ice. Nine quality-control sets consisting of 27 serum samples were prepared by staff at Johns Hopkins University. The first sample in each quality-control set was a replicate of pooled samples of serum collected during the CLUE I survey from ten participants who lived outside the geographical limits of the cohort definition. The second and third sample in each quality-control set were replicates from nine pooled samples of two or three participants. We used the first sample in each quality-control set to calculate a between-set coefficient of variation. The second and third samples in each quality-control set were used to calculate a within-set coefficient of variation as described by Bush.⁷ The nine quality-control sets were masked by assigning an unused study number to each set; the sets were then interspersed in the study samples submitted for analysis.

All serum samples were analysed⁸ under masked conditions at the National Center for Environmental Health, Centers for Disease Control and Prevention. A reagent blank (to check for contaminants) and an internal laboratory quality-control sample (spiked bovine serum)⁹ were analysed with every ten study serum samples. Solid-phase extraction was carried out and then each sample was analysed on two separate gas chromatographs with electron-capture detection. The chromatographs used different columns (DB5 and DB1701) to reduce interference and improve selectivity. Results were obtained for: four DDT-related compounds (*o,p'*-DDT, *p,p'*-DDT, *o,p'*-DDE, *p,p'*-DDE), 28 PCB congeners, two lindane-related compounds (lindane [γ -hexachlorocyclohexane] and β -hexachlorocyclohexane), four technical-grade chlordane-related or heptachlor-related compounds (transnonachlor, heptachlor, heptachlor epoxide, oxychlordane), one aldrin-related compound (dieldrin), hexachlorobenzene, and mirex.⁸ The serum sample from one control was not successfully analysed. Thus, 73 complete case-control sets (one case and two controls) and one set with one case and one control were available for our analysis. We report results for total DDT and total PCBs only; detailed results for the other organochlorine compounds will be reported elsewhere.

Serum samples were analysed for total cholesterol and triglycerides, and total lipids were calculated by a standard formula to correct for differences in recent food intake.⁹ We

calculated a lipid-corrected total PCB variable by dividing each congener by the total lipid value and adding them together. A lipid-corrected total DDT variable was calculated by addition, after dividing each DDT compound by the total lipid value. Before addition, values for *o,p'*-DDE and *p,p'*-DDE were converted into their DDT equivalents (DDE X 354.5/318). The DDT metabolite, *p,p'*-DDE, made up 82% of the DDT compounds and strongly correlated with the total DDT variable (Spearman $r=0.99$ among controls). All cases and controls had total PCB and DDT values above zero, which moderately correlated with each other (Spearman $r=0.41$ among controls). The within-set coefficients of variation were 8.5% and 18.0% for lipid-corrected PCBs and DDT, respectively, and the between-set coefficients of variants were 12.9% and 13.0%, respectively.

We did not eliminate values below the formal method detection limit.⁸ The formal method detection limit was designed to eliminate 99.86% of false-positive results, but this conservative definition can also result in loss of valid data. When 50% of the formal method detection limit was assigned to all samples below the formal detection limit, the new PCB and DDT variables correlated strongly with their counterparts that used all available data as described above (Spearman $r=0.95$ and 1.0, respectively, among controls).

Serological analysis of Epstein-Barr virus

Mueller and colleagues¹⁰ postulated that exposure to ubiquitous immunosuppressive agents in the environment may reactivate latent Epstein-Barr virus infection and contribute to increased risk of non-Hodgkin lymphoma. We used Epstein-Barr virus serological status of study participants, initially reported by Bush,⁷ to assess potential interactions with serum concentrations of organochlorines. IgG antibody titres were measured against the Epstein-Barr virus early antigen (EBV-EA) and viral capsid antigen by immunofluorescence.¹¹ Because only the EBV-EA was associated with risk of non-Hodgkin lymphoma,⁷ it is the only EBV measure we report (seronegative: reciprocal titre <20; seropositive: reciprocal titre ≥ 20 , diffuse and restricted components combined). EBV-EA data were available for 73 of the 74 cases and for 145 of the 147 controls; data for two controls were not used in the analysis because there was no information on this variable for their matched case.

Statistical analysis

Summary organochlorine data for cases and the average of the two controls in each set are described by the median value (10th, 25th, 75th, 90th percentiles). We tested case-control differences by the Wilcoxon signed rank test. We used conditional logistic regression to analyse the association between risk of non-Hodgkin lymphoma and total lipid-corrected serum concentrations of DDT and PCBs divided into quartiles (based upon fourths of the distribution among controls). Statistical significance was calculated by the likelihood ratio test based on

	Cases (n=74)	Controls (n=147)
Mean (SD) age in years at enrolment	52.9 (13.2)	52.5 (13.8)*
Sex		
Male	35 (47%)	69 (47%)
Female	39 (53%)	78 (53%)
Education (years)		
≥ 12	47 (64%)	73 (50%)
<12	27 (36%)	74 (50%)
Cigarette use		
Current	20 (27%)	50 (34%)
Former	19 (26%)	38 (26%)
Never	35 (47%)	59 (40%)

*Mean of average of matched controls.

Table 1: Demographic characteristics of cases of non-Hodgkin lymphoma and matched controls identified from a prospective cohort enrolled in 1974, Washington County, Maryland, USA

Organochlorine	Cases (n=74)	Controls (n=147)*	p†
DDT (ng/g lipid)	3150 (1330, 1850, 5110, 6450)	2770 (1300, 2030, 3810, 5510)	0.20
PCB (ng/g lipid)	951 (608, 772, 1270, 2030)	864 (605, 666, 1080, 1270)	0.0014

Values are median (10th, 25th, 75th, 90th percentiles).

*Calculated from average of matched controls. †Wilcoxon signed rank test.

Table 2: Distribution of total lipid-corrected DDT and PCB serum concentrations in cases of non-Hodgkin lymphoma and matched controls

the model. This approach results in deletion of all participants within a set when data are missing for either the case or both controls. Tests for trend were calculated by a variable equal to the mean organochlorine concentration in each quartile, divided by the mean concentration in the first quartile. Similar trend results were obtained with PCB or DDT as continuous variables. CLUE I questionnaire data used in the analysis were: years of education (<12 years, ≥12 years), ever smoked cigarettes (yes/no), currently smoking cigarettes (yes/no), and potential for occupational exposure to PCBs (yes/no, based upon review of self-reported current occupation and industry).

Results

Among the 74 cases, the mean time to a diagnosis of non-Hodgkin lymphoma after enrolment into the cohort in 1974 was 12.1 years (SD 5.2, range 1–20). 99% of cases and their 147 matched controls were white. Age at enrolment and sex distribution were the same among cases and controls, and smoking habits were similar in each group. A moderately higher proportion of cases than controls were high-school graduates (table 1).

There were no significant differences in total lipid-corrected serum concentrations of DDT between cases and controls (table 2). By contrast, PCB concentrations were significantly higher in cases than in controls (table 2). The risk of non-Hodgkin lymphoma increased only weakly and non-significantly with increasing DDT concentrations, whereas the risk increased significantly with increasing PCB concentrations (table 3). When each measure was adjusted for the other, the association between non-Hodgkin lymphoma and DDT weakened but PCB effects changed only slightly (table 3). The DDT variable did not improve the fit of a model containing only the PCB variable (likelihood ratio test: $\chi^2=0.18$, 3 df, $p=0.98$) and was excluded from further analyses.

Of the nine additional organochlorine compounds measured, two (mirex and γ -hexachlorocyclohexane) were detected in fewer than 10% of cases and controls and were excluded from the analysis. There was

no significant association between increased risk of non-Hodgkin lymphoma and these organochlorines alone or in combination with other compounds in the same class—eg, technical-grade chlordane-related compounds—either with or without adjustment for PCBs.

The association of PCBs and risk of non-Hodgkin lymphoma was not diminished after adjustment for education (odds ratio by PCB quartile: 1.0; 1.4 [95% CI 0.5–3.6]; 2.9 [1.1–8.1]; 4.3 [1.6–11.8]; p for trend=0.0027), cigarette use, or any other organochlorine compound, separately or together. Exclusion of 25 cases of non-Hodgkin lymphoma without a pathology slide available for review had little impact on the risk of non-Hodgkin lymphoma for the remaining participants (odds ratio by quartile: 1.0; 1.1 [0.4–3.0]; 3.4 [1.0–11.8]; and 4.3 [1.2–14.7]; p for trend=0.017). Results were not attenuated after exclusion of two cases diagnosed within 2 years of enrolment into the cohort. We identified five participants (one case, four controls) who had potential for occupational PCB exposure; concentrations of PCB and DDT among these participants were similar to the distribution in the entire study population and their exclusion from the analysis did not affect the results. When we used quartile cut-off points based upon the PCB distribution in all controls, PCB-associated risks for non-Hodgkin lymphoma were similar for men and women (odds ratio 1.0; 1.6 [0.3–8.9]; 2.2 [0.4–11.2]; 4.8 [0.8–28.9]; p for trend=0.022 vs 1.0; 1.2 [0.4–3.6]; 4.4 [1.1–17.4]; 4.6 [1.4–15.6]; p for trend=0.013), and changed little with sex-specific cut-points.

EBV-EA and PCB data were available for 70 complete sets and three sets with one case and one matched control. Within this subgroup, EBV-EA seropositivity (present in 16 of 73 cases and 14 of 143 matched controls) was associated with an odds ratio of 2.6 (1.2–5.9) and PCB quartile-associated odds ratios were 1.0, 1.5 (0.6–3.8), 3.4 (1.2–9.7), and 5.2 (1.8–14.5). There was a significant positive effect of PCBs (classified into low and high according to the median value in the controls) on the risk of non-Hodgkin lymphoma among EBV-EA-seronegative participants, which increased among seropositive participants (table 4). There was evidence of a multiplicative interaction ($p=0.025$): the combined effect of EBV-EA seropositivity and a high concentration of PCB (odds ratio 22.3) was greater than expected based upon the product of their independent effects (1.0 and 2.8; table 4). This interaction was influenced more by the association between PCB concentration and EBV-EA seropositivity among controls

Quartile	Organochlorine concentration			Cases (n=74)	Controls (n=147)	Matched odds ratio (95% CI)‡	Matched, adjusted odds ratio (95% CI)§
	Range (ng/g lipid)*	Mean (ng/g lipid)*	Mean (ng/mL)†				
DDT							
1	180–1740	1200	8.7	14	37	1.0	1.0
2	1760–2660	2210	16.3	16	37	1.2 (0.5–2.8)	1.1 (0.4–2.7)
3	2690–4020	3230	24.0	19	37	1.4 (0.6–3.3)	1.1 (0.4–2.7)
4	4140–20 500	6550	49.1	25	36	1.9 (0.8–4.5)	1.2 (0.5–3.0)¶
PCB							
1	247–641	526	3.8	10	37	1.0	1.0
2	649–806	727	5.5	13	37	1.3 (0.5–3.3)	1.3 (0.5–3.3)
3	814–1060	924	6.7	21	37	2.8 (1.1–7.6)	2.7 (0.9–7.8)
4	1070–2070	1430	10.3	30	36	4.5 (1.7–12.0)**	4.1 (1.4–11.9)††

*Lipid-corrected serum concentrations. †Uncorrected serum concentrations. ‡Conditional logistic regression of 73 sets containing one case and two matched controls and one set containing one case and one matched control. §DDT and PCB risk estimates adjusted for each other. || p for trend=0.15, calculated by conditional logistic regression for a variable equal to the mean concentration in each quartile divided by the mean concentration in quartile 1. ¶ $p=0.87$. ** $p=0.0008$. †† $p=0.002$.

Table 3: Total lipid-corrected serum concentrations of DDT and PCB and risk of non-Hodgkin lymphoma

	EBV-EA			
	Reciprocal titre <20		Reciprocal titre ≥20	
	Cases/ controls	Odds ratio (95% CI)*	Cases/ controls	Odds ratio (95% CI)*
PCB (ng/g lipid)				
<810	18/62	1.0	4/11	1.0 (0.3-3.6)
≥810	39/67	2.8 (1.2-6.2)	12/3	22.3 (4.3-115.0)†

EBV-EA and PCB data available for 70 complete sets with one case and two controls and three sets with one case and one control.

*Matched odds ratio by conditional logistic regression. † $p=0.025$ for multiplicative interaction.

Table 4: Interaction between total lipid-corrected PCB serum concentration and EBV-EA for risk of non-Hodgkin lymphoma

than among cases (table 4). Among individuals who were seronegative for EBV-EA, a dose-response relation between risk of non-Hodgkin lymphoma and PCB quartiles was present (odds ratios: 1.0; 1.5 [0.5-4.1]; 2.9 [1.0-8.9]; 4.2 [1.4-13.1]).

Discussion

In this nested case-control study, a significant association between DDT and risk of non-Hodgkin lymphoma, our primary a priori hypothesis, was not found. However, serum concentrations of PCB were strongly associated with risk of non-Hodgkin lymphoma. In addition, there was evidence suggesting that seropositivity for the EBV-EA potentiated the effects of serum PCBs, but this effect was based on only a small number of participants and the magnitude of the effect may have been overestimated.

Our study has several strengths. Disease status could not have biased the results because serum samples were collected from participants when they were healthy. We used an analytical method to measure organochlorines that excluded many interfering compounds⁸ and corrected values for serum lipids. The serum concentrations of total PCBs among controls (median 6.3 ng/mL) were similar to those found in other US populations in the 1970s without occupational or exceptional environmental PCB exposures.¹² The similar association between serum concentration of PCB and risk of non-Hodgkin lymphoma in men and women provides evidence of internal consistency.

Our finding of an association between risk of non-Hodgkin lymphoma and serum concentrations of PCB accords with those of Hardell and colleagues,¹³ who measured organochlorine residues in adipose tissue from incident, untreated cases of non-Hodgkin lymphoma and controls in a small hospital-based case-control study in Sweden. However, results from retrospective cohort mortality studies of electrical-capacitor-manufacturing workers exposed to PCBs¹⁴⁻¹⁷ and a study of cancer incidence and mortality among Swedish fishermen who consume PCB-contaminated fish from the Baltic Sea⁸ show only weak and inconsistent evidence of increased risk of lymphatic/haematological malignant diseases (LHM). Significantly increased risks were reported for LHM, mainly Hodgkin's disease, among female capacitor-manufacturing workers¹⁴ and for mortality from multiple myeloma among Swedish fishermen.¹⁶ Non-significant increases in LHM¹⁴ and non-Hodgkin lymphoma¹⁷ have been found among male capacitor-manufacturing workers. By contrast, two studies found no evidence of increased LHM among workers exposed to PCBs.^{15,16} Overall, there were few expected cases of non-

Hodgkin lymphoma in these studies: cancer mortality rather than incidence was the outcome measure in the studies of capacitor-manufacturing workers,¹⁴⁻¹⁷ and in two reports,^{14,16} participants were relatively young when their vital status was ascertained, so the risk of cancers with long-term latency could not be assessed. Nevertheless, some of the workers in the capacitor-manufacturing groups had documented serum concentrations of PCB at least one order of magnitude higher than the concentrations in the top quartile of our study,¹⁴⁻¹⁶ and it is noteworthy that these studies found no increased risk of non-Hodgkin lymphoma.

It is possible that confounding was present in our study—ie, that an unrecognised risk factor was associated with PCB concentrations, and, more strongly, with risk of non-Hodgkin lymphoma. For example, there may be unmeasured fat-soluble compounds in the environment that bioaccumulate in parallel with PCBs and have a role in the aetiology of non-Hodgkin lymphoma. In addition, diet (fish, meat, milk and dairy products)¹⁹ and body weight²⁰ influence PCB body burden and may be associated with the disease (SHZ, unpublished observations),²¹⁻²⁵ but could not be adjusted for in our study because of lack of data. But the magnitude of the risks observed with these variables has generally been two-fold or less and is not high enough to have substantially confounded the strong relation between PCBs and non-Hodgkin lymphoma reported here.

PCBs consistently cause excess neoplastic liver nodules and hepatocellular carcinoma in animals,²⁶ and are classified by the International Agency for Research on Cancer as probable human carcinogens.²⁷ PCBs can act as tumour promoters,²⁶ can alter immune function in animals,²⁸ and may cause subtle immunological changes in exposed human beings.^{29,30} Changes in the immune system are an important mechanism in lymphomagenesis, but only severe changes in immune function have been linked to non-Hodgkin lymphoma.³¹

We found a non-significant positive association between DDT and risk of non-Hodgkin lymphoma that was greatly diminished after adjustment for PCBs. Although our analysis of DDT was less precise than that of PCBs (within-set coefficient of variation 18.0% vs 8.5%), it is unlikely that a coefficient of variation of this magnitude would have substantially attenuated a strong association between risk of non-Hodgkin lymphoma and DDT. Similarly, Hardell and colleagues³ found no significant difference in concentration of *p,p'*DDE in adipose tissue between cases of non-Hodgkin lymphoma and controls. However, several case-control interview studies of non-Hodgkin lymphoma have reported small risk excesses with self-reported or proxy-reported agricultural exposure to DDT, with odds ratios of 1.3-1.8 that were generally not adjusted for other pesticides.^{4-6,32} Although our findings suggest that a link between non-Hodgkin lymphoma and DDT in the general population is unlikely, this hypothesis is worthy of further consideration, given limitations in the available database.

Because our findings were not specific a priori hypotheses, they should be regarded as hypothesis-generating. Before causal inferences can be made about PCB exposure and increased risk of non-Hodgkin lymphoma, these results require replication and potential confounding by risk factors not ascertained here should be examined. Moreover, the inconsistency between our

findings and those from studies of PCB-exposed occupational cohorts needs to be explained; and the biological plausibility of this association requires further investigation.

Contributors

Nathaniel Rothman was the principal investigator for this project and was involved in all components of the study. All authors contributed to the protocol development, data interpretation, and writing of the paper. George Comstock and Kathy Helzlsouer were responsible for the development and maintenance of the CLUE cohort studies. Paul Strickland provided oversight for the laboratory analyses. David Bush coordinated the selection of cases and controls and histology review, and provided data on Epstein-Barr virus serology. Kenneth Cantor, Aaron Blair, David Bush, Kathy Helzlsouer, Shelia Zahm, Robert Hoover, George Comstock, and Paul Strickland provided input into the study design and statistical analyses. John Brock and Larry Needham were responsible for the assessment of organochlorine exposure. Gary Pearson was responsible for the laboratory analysis of Epstein-Barr virus serology.

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